animal] mammal with a substance comprising a physiologically acceptable [plant] material from a plant containing the NEPA expressed by the plant, in combination with an orally effective adjuvant, said combination causing an immune response to oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA alone.

Please rewrite Claim 3 as follows:

Claim 3 (amended)

The method of Claim 1 wherein the [animal is made immunoreceptive to the] NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue hemoragic fever, tetanus, staphylococcus aureous, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever [by feeding the substance to the animal in conjunction with an adjuvant that renders the animal immunoreceptive to the NEPA].

Please cancel Claim 4.

In Claim 11, please replace "*solanaceae*" with --*Solanaceae*--.

Remarks

The Examiner has objected to the declaration on the ground that the signature of the first inventor, Yasmin Thanavala, is missing.

The objection should be withdrawn.

The joint applicants executed separate declarations and both were submitted with the "Statement in Compliance" filed February 17, 2000. Execution of separate declarations is

clearly permitted. See e.g. MPEP 605.04(f), last paragraph. The Examiner may have overlooked the fact that two declarations accompanied the "Statement in Compliance".

Claims 1 and 3 have been rejected under 35 U.S.C. 112 for being indefinite.

The rejection should be withdrawn.

The Examiner states that "providing an immune response" is indefinite. With due respect to the Examiner, the phrase is not indefinite. A term that is generic is not the same as a term that is indefinite (See MPEP 2173.04). One skilled in the art knows how to determine the types of immune response listed by the Examiner and there is no reason that the invention should be restricted to any one of them. None of the claims are indefinite.

The Examiner further states that the phrases "in an animal made immunoreceptive to the NEPA" and "wherein the animal is made immunoreceptive to the NEPA" render the claims indefinite. Again the Examiner is improperly equating breadth with ambiguity. None of the claims are rendered indefinite because of the language in question. The objection is nevertheless rendered moot since the claims have been amended to the use of an adjuvant for that purpose.

With due respect to the Examiner, having a healthy immune system does not necessarily mean that an individual is immunoreceptive to an antigen no matter how it is presented. There are many antigens that raise an immune response when injected that do not raise an immune response when presented orally. The present invention employing an oral adjuvant permits an immune response to be raised to an antigen that is presented orally when such an antigen presented orally would not normally raise such a response.

The rejection with respect to Claim 11 is not understood. *Solanaceae* is a Latin term for a family in biological classification and is properly italicized. There is no ambiguity. If the rejection was based upon whether or not the term was capitalized or italicized or underlined, this would be a formal objection and would hardly support a rejection under 35 U.S.C. 112.

Claims 1, 3, and 5-12 have been rejected under 35 U.S.C. 103 as being unpatentable over U.S. Patent 5,935,570 to Koprowski et al. in view of Stites et al.

This rejection should be withdrawn.

Koprowski et al., contrary to statements by the Examiner, do not disclose or suggest feeding a plant material containing NEPA expressed by the plant as required by the present claims. The Koprowski et al. plant material is not genetically altered as asserted by the Examiner. The plants of Koprowski et al. are simply hosts for a parasitic microorganism expressing a bioactive compound (and as such the plants would not usually grow happily). The only specific example in Koprowski et al. is for a microorganism that expresses a gene for rabies N protein. Since rabies is known to have the ability to invade a mammal by means other than through a breach in the skin and can raise an immune response enterically without an adjuvant or prior immunization, as evidenced by Koprowski, it is not covered by the present claims since it does not meet the criteria for non-enteric pathogens in the claims.

Koprowski et al. suggest that their method has wide application, e.g. for treatment of viral infections, bacterial infections, fungal infections, protozoan infections, diabetes, immune disorders, cancer and heart disease. Koprowski et al. more specifically suggest that their method could be used for mucosal pathogens, e.g. rabies, respiratory syncytial virus, cholera, typhoid

fever, herpes simplex types I and II, tuberculosis, pathogenic pneumococci, human immunodeficiency virus-1 (HIV-1) and human immunodeficiency virus-2 (HIV-2).

The only specific example given is for rabies. There is no enablement for the other suggested applications. If the disclosure actually enabled everything suggested, oral vaccines effective against AIDS, cancer, and herpes, among many others, would be made available simply by following the teachings of the Koprowski et al patent. This is simply not the case.

Koprowski et al. certainly do not enable or even reasonably suggest application for orally raising an immune response to antigens of the non-enteric pathogens in accordance with the method of the present claims. The suggestion by Koprowski et al. that an adjuvant be used is a gratuitous statement applied across the entire non-enabled spectrum of the Koprowski et al. disclosure. There is no suggestion or teaching of any specific adjuvant that would have would have any effect whatsoever **upon oral immune response to antigens** of the non-enteric pathogens in the present claims and there is no suggestion that any adjuvant would have any effect upon an antigen that is expressed by and often contained within the structure of plant material. Adjuvants that can be used in injected vaccines rarely have any significant effect when administered orally.

Stites et al. add nothing to cure the inadequate teachings and suggestions of Koprowski et al. Stites does not suggest anything whatsoever concerning orally effective vaccines against non-enteric pathogens as presently claimed and certainly suggests nothing suggesting that an NEPA would orally raise a highly effective immune response in the presence of a suitable adjuvant as presently claimed.

The rejection should be withdrawn.

Claims 1-2 and 4-12 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,914,123 to Arntzen et al., and U.S. Patent 5,935,570 to Koprowski et al. in view of Stites et al. Basic and Clinical Immunology, pp. 723-741.

This rejection should be withdrawn.

Arntzen et al. teach a method for making a transgenic plant, e.g. tobacco, tomato or potato that express antigens from certain pathogenic organisms, especially HBsAg as set forth in the specific examples.

Arntzen et al. do not teach that ingestion of a tomato or potato (and certainly not the tobacco because it is toxic) would cause an immune response to HBsAg.

Arntzen et al. recognize that not all antigens would cause an immune response if ingested.

Arntzen et al. say in column 15 beginning at line 27,

"The vaccines are conventionally administered parenterally, by injection, for example either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, ***in some cases***, oral formulations or aerosols." (emphasis added).

While Arntzen et al. suggest that tomato juice containing HBsAg might be used as a vaccine, in fact Arntzen provides no supporting data showing any immune response whatsoever to tomato juice or any other plant containing HBsAg. To the extent that Arntzen teaches that tomato juice or any other plant material containing HBsAg can be used as a vaccine, it is an inoperative reference since there is no teaching or suggestion as to how that might be done. ***Simply ingesting the plant material, as suggested by Arntzen et al., does not confer immunity***.

There is good reason for Arntzen's omission of data showing immune response to HBsAg by ingesting food material containing it, since prior to the present invention, in fact, there was little if any immune response whatsoever to HBsAg in orally ingested tomato juice or any other plant expressing HBsAg. The response, if any, is clearly insufficient for that purpose.

Reference to the examples in the present specification clearly illustrates that priming of the subject of the immunization is required by either pre-vaccination or the use of an effective adjuvant and **an adjuvant is required by the present claims**. Arntzen et al. suggest neither pre-vaccination nor an adjuvant. Arntzen et al. doesn't suggest an adjuvant for any purpose whatsoever and certainly does not suggest a combination with an adjuvant that permits the obtaining of a high immune response to orally administered antigen as required by the present claims.

Arntzen discloses or suggests no way in which a high immune response could be orally obtained.

In any case there is certainly no suggestion of the enhanced immune response to NEPA's in orally administered plant material expressing the NEPA, as provided by the method presently claimed.

The Examiner states that Koprowski "teaches a method for genetically altering the plant material of solanaceous plants..." The Examiner's statement is inaccurate. Koprowski et al. do not teach or suggest any method for making a transgenic plant but teaches a microorganism expressing a bioactive compound, e.g. an immunogenic rabies polypeptide. The microorganism may then be used to infect a plant as a parasite but does not alter the genetic character or

expression of the plant. Koprowski et al. therefore does not cure any of the critical defects of Arntzen et al.

None of the references, alone or in combination, enable the raising of an oral immune response to NEPA **expressed in plants** and certainly do not suggest that an enhanced oral response to an NEPA could be obtained when the oral administration was conducted in conjunction with a suitable oral adjuvant.

Stites et al. add nothing to cure the inadequate teachings and suggestions of Arntzen et al. and Koprowski et al. Stites does not suggest anything whatsoever concerning orally effective vaccines against non-enteric pathogens as presently claimed and certainly suggests nothing suggesting that an NEPA would orally raise a highly effective immune response in the presence of a suitable oral adjuvant as presently claimed.

Claims 2 and 4 of the above application have been rejected as being in conflict with Application No. 09/418,177.

It is requested that the rejections over copending application 09/418,177 be temporarily held in abeyance since application 09/418,177 is being allowed to go abandoned by failure to respond. The rejections will thus be moot. In any case, the claims have been amended so that any conflict has been eliminated.

Claims 2 and 4 have been rejected on the grounds that they conflict with claims of Application No. 09/420,695.

The claims have been amended so that there is no longer any conflict.

The rejection based upon double patenting under 35 U.S.C. 101 due to conflict of claims has thus been eliminated.

It is requested that this rejection be withdrawn.

Claims 1-12 have been rejected for obviousness type double patenting over claims 1-19 of copending Application 09/464,414.

The claims of 09/464,414 claim subject matter where an animal is made immunoreceptive by immunization prior to feeding plant material containing HBsAg. The claims as amended no longer claim subject matter where an animal is made immunoreceptive by immunization prior to feeding plant material containing HBsAg. The present claims are restricted to the use of an adjuvant. The claims of 09/464,414 do not require adjuvant. The present claims and the claims of 09/464,414 thus no longer overlap and are not obvious in view of each other.

Claims 1-12 have been provisionally rejected for obviousness type double patenting over Claims 1-20 of copending Application 09/420,695.

A terminal disclaimer has been provided overcoming this rejection.

Claims 1-12 have been provisionally rejected for double patenting in view of Claims 1-20 of copending Application 09/418,177.

Application 09/418,177 is being permitted to go abandoned. The rejection will thus be moot before the issuance of the present application.

All rejections have been addressed and overcome by the foregoing amendments and remarks. It is therefore courteously requested that all rejections be withdrawn and all claims be allowed.

Respectfully submitted,

Dated: July 11, 2000

Michael L. Dunn
Attorney for Applicant(s)
Reg. No. 25,330
P.O.Box 96
Newfane, New York 14108
Telephone: (716) 433-1661

MLD